marked up copy

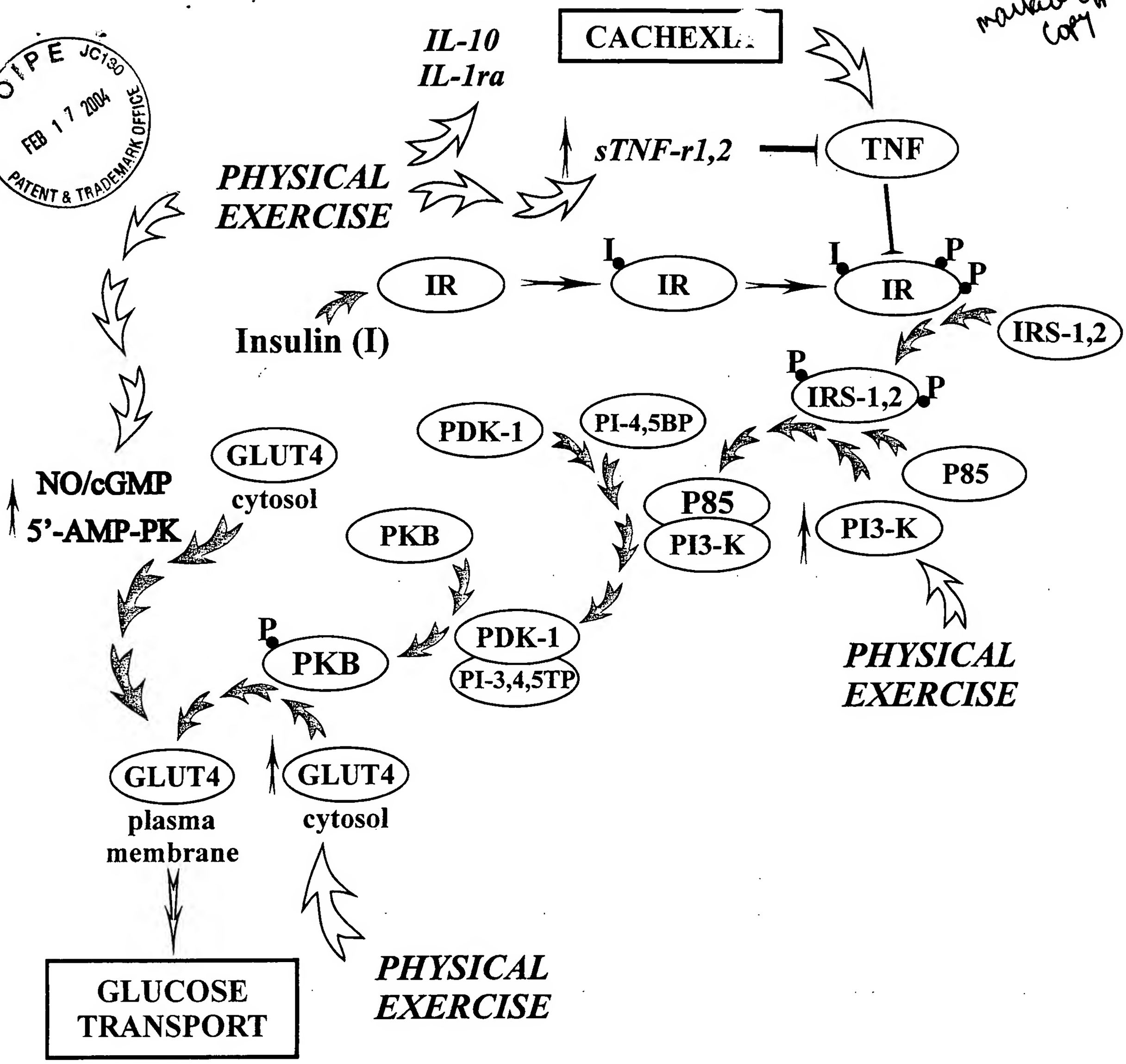

Figure 1. The effect of cachexia and physical exercise on the GLUT4 activation pathways.*
~~Inflammation-induced TNF blocks activity of the insulin-activated IR. Physical exercise-suppression of the~~ inflammatory responses (induced IL-10, IL-1ra, sTNF-r1,2) may block the synthesis/release of TNF thereby attenuating production of insulin-resistance. Activation of the GLUT4 pathways through enhanced NO, cGMP, 5'-AMP-PK activity, GLUT4 synthesis, PI-3 kinase activity, and GLUT4 translocation by physical exercise will enhance insulin sensitivity and possible prevent or reverse cachexia-associated insulin resistance.

*Because no single experiment has addressed all components of the illustrated molecular pathways, the interactions illustrated in Figures 1 through 4 are a composite of many in vivo and in vitro experiments involving many cell types (see text). These hypothetical constructs illustrate how exercise might be able to attenuate cancer- or cachexia-associated fatigue by activating GLUT4 translocation through non-insulin pathways, by enhancing PI3-K and GLUT4 synthesis, and by activating protein synthesis via Ca++ and ROS-mediated activation of the MAPK and JNK-MAPK pathways. Exercise also may decrease inflammatory responses through enhanced production of sTNF-r1, sTNF-r2, IL-10, and IL-1ra.

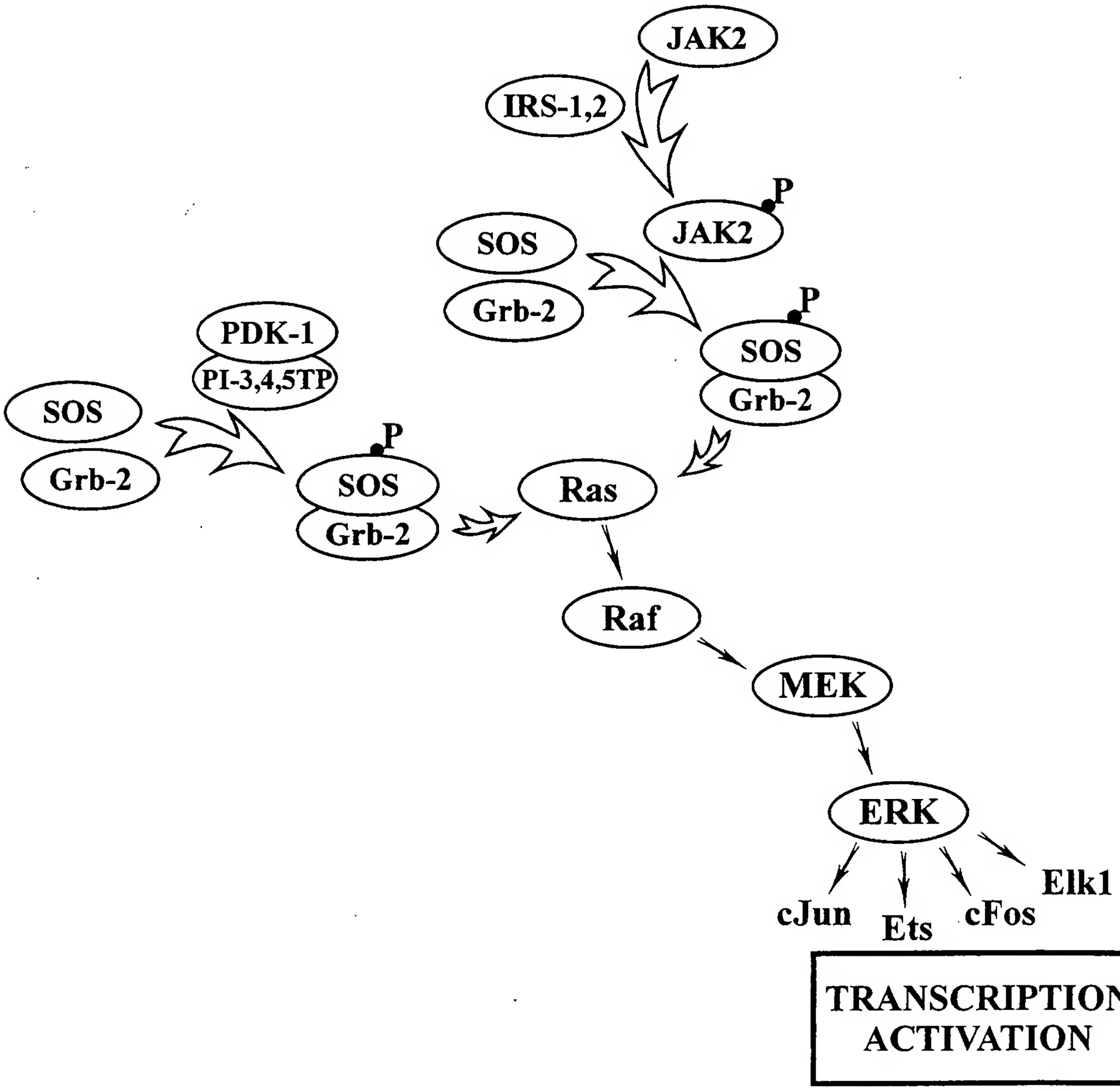

Figure 2. Insulin-mediated activation of the MAPK pathway of transcription activation. ~~Both the activated IRS-1,2 (through activated JAK2) and the PDK-1.3,4,5TP complexes can activate the~~ SOSGrb-2 complex which in turn activates ras of the MAPK pathway, resulting ~~in enhanced protein synthesis~~.

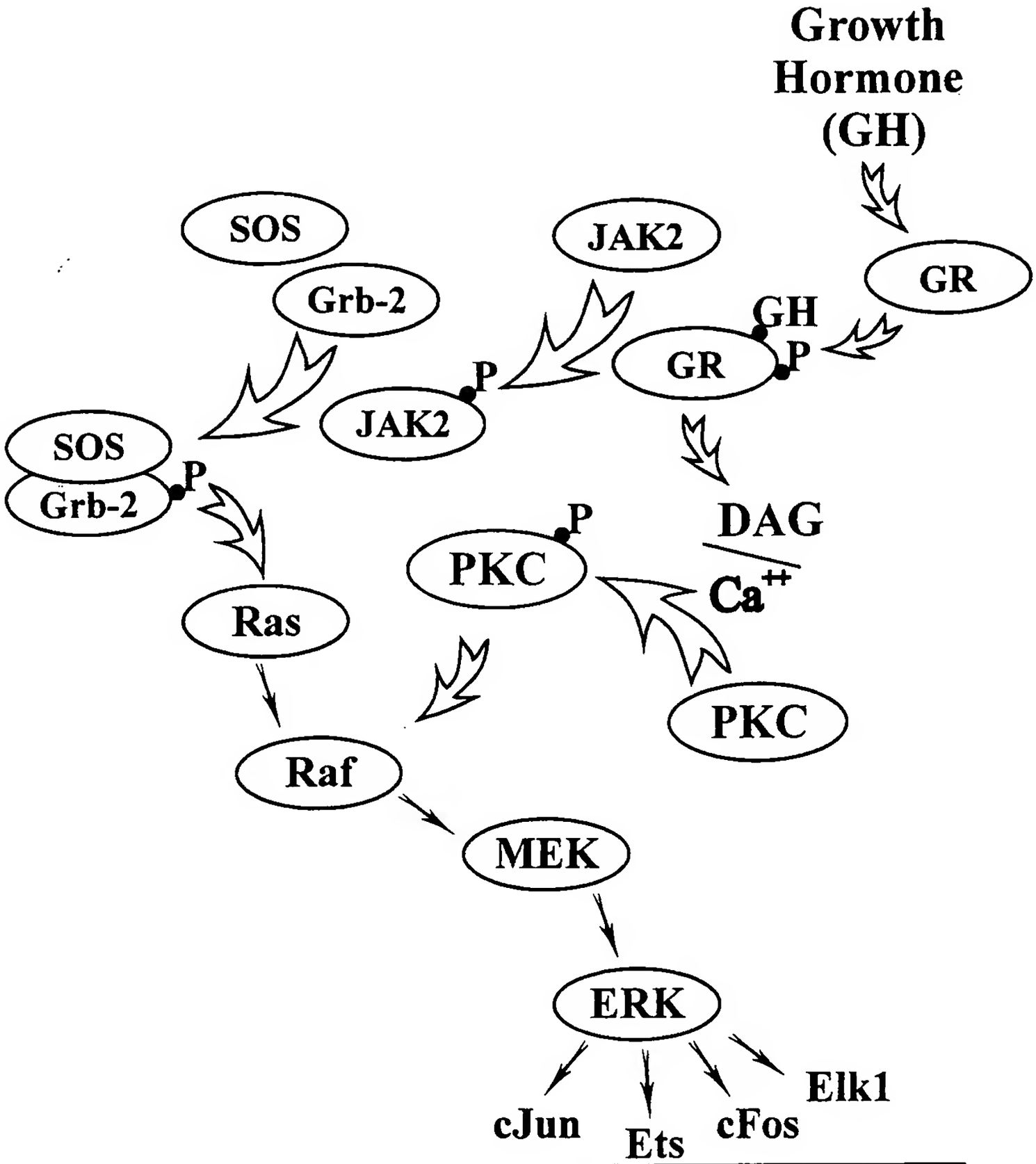

Figure 3. Growth-hormone (GH)–mediated activation of the MAPK pathway of transcription activation. ~~The activated growth hormone receptor (GR) activates JAK2 which mediates the activation~~ of ras via the SOSGrb-2 complex. Activated GR also ~~stimulates the release of~~ Ca^{++} into the cytosol (via DAG) which activates ~~PKC. PKC~~ in turn activates raf of the MAPK pathway; ~~activation of both ras and raf results in enhanced protein synthesis~~.

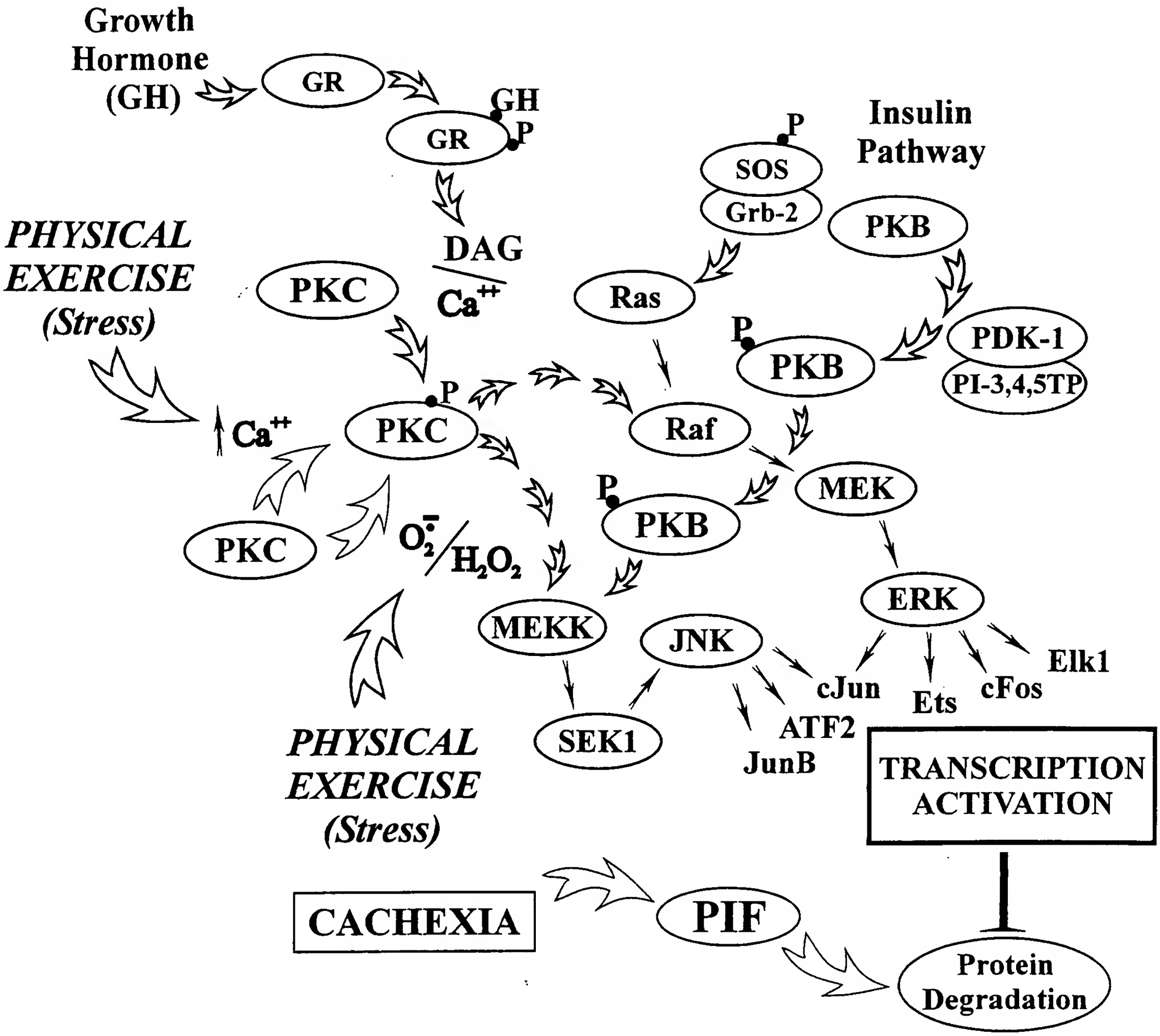

Figure 4. Interactive effects of physical exercise, insulin, and growth hormone on activation of the SAPK and MAPK pathways of transcription activation.
~~PKC is activated by physical exercise through enhanced Ca^{++} and ROS as well as by growth hormone~~ through DAG/Ca^{++}. ~~PKC in turn~~ activates the SAPK and MAPK pathways ~~by activating~~ MEKK and raf, respectively. By enhancing insulin sensitivity ~~and activating~~ SAPK and MAPK independently if insulin and growth hormone, physical exercise ~~should greatly~~ enhance rates of protein ~~synthesis~~ beyond that expected by insulin or growth ~~hormone~~ alone; resulting in an attenuation of prevention of cachexia-associated ~~muscle~~ ~~wasting~~ and fatigue.

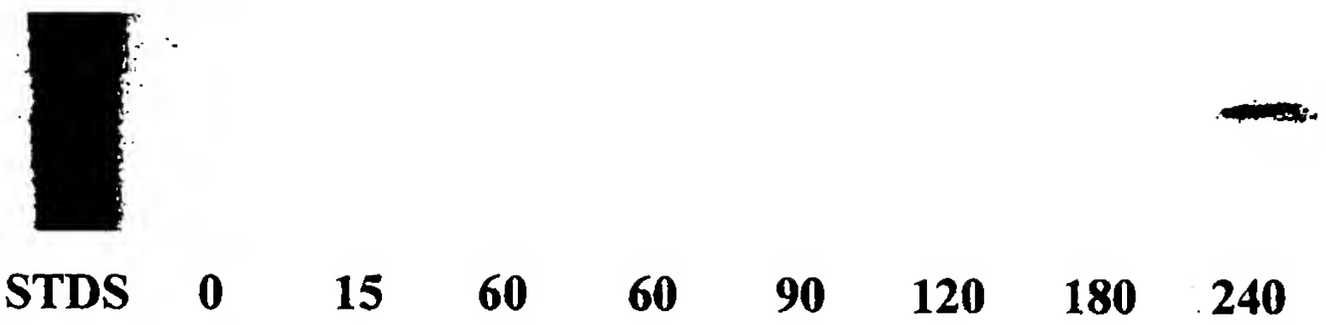

Figure 5. The effect of acute running exercise on Jun content of lung nuclei from rats. ~~Rats were exercised for 60 minutes and 3 rats killed at each time period of 0, 15, 30, 60, 90, 120, 180, 240~~, and 300 minutes from the start of the exercise. ~~Lung nuclei were probed for jun~~ using anti-cJun/AP-1 antibody in a western blot procedure. ~~The blot was digitized~~, converted to grayscale, and ~~the 35-45 kDa~~ region of the blot ~~which included~~ the immunoreactive protein was then printed using an ~~HP~~ Photosmart 1215 printer at highest ~~resolution~~.